REMARKS

Claims 1-15 and 17-20 are pending in this application. Claims 1-12 and 18-20 stand rejected and claims 13-15 and 17 were withdrawn from consideration. Reconsideration and allowance of the claims is respectfully requested in view of the following remarks.

Applicants also wish to draw to the Examiner's attention co-pending application US Application No. 11/579,675 which application is titled "Antisolvent Emulsion Solidification Process."

REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-3, 5-8, 10, 18 and 20 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jakupovic et al. (US Patent 6,221,398) in view of Subramaniam et al (US Patent No.: 6,113,795). Applicants traverse this rejection for the reasons provided herein below.

This instantly claimed process provides a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a membrane into one or more antisolvents, or vice versa. The membrane is used as a precision dosing device allowing for efficient micromixing of the liquid medium comprising at least one dissolved compound and one or more antisolvents and continuous operation (see, e.g., paragraph [47] of the published US patent application, Publication No.: US2006/018280800). In contrast to a batch process, the instantly claimed process can be easily scaled up for commercial production while maintaining robust control of the particle size (see, e.g., paragraph [15]) by allowing for the ratio of solvent to antisolvent to be controlled thereby resulting in more uniform particle size (see, e.g paragraphs [15] and [55]) and avoiding uncontrolled precipitation of solids and the formation of agglomerated particles (see, e.g., paragraphs [15], [20]). In a batch process, such as Jakupovic et al, the ratio of solvent to antisolvent varies and accordingly, so will the particle size.

Jakupovic et al relates to a batch process for producing a pharmaceutical powder for inhalation. In Jakupovic et al an inhalation compound is dissolved in a solvent which is introduced in droplet form or as a jet stream into an antisolvent (which is miscible with the solvent) under agitation and non-supercritical conditions (see column 2, lines 26 to 34 of Jakupovic et al). The solution is introduced into the antisolvent, for example, through a

porous filter or one or more nozzles (see column 2, lines 63 to 65). Exemplified are batch-type preparation processes which use Pyrex Glass Filters having a pore index from 10 microns to 160 microns (see Examples 1-8, columns 5 and 6) which resulted in particles having a mass median diameters (MMD) smaller than the pore size of the filter (MMDs ranged from 2.49 microns to 5.2 microns, see Examples 1-8, columns 5 and 6). Surprisingly, the instantly claimed process using a pore size of up to 3 μm pores can produces particles having a d50 larger than the pore size. For example, use of a 1 μm pore filter, resulted in an average crystal size of d50 of 40 μm (see Example 1, paragraphs [79] -[82]) and a d50 ranging from 7 to 42 μm depending on the flow rate (see Example 2, paragraphs [83] to [89]). Jakupovic et al does not teach or suggest that Pyrex Glass Filters can be easily exchanged for a membrane or that the method can be used to produce particles larger than the pore size of the filter used. Accordingly, Jakupovic et al does not render the claimed invention obvious.

As noted by the Examiner, Jakupovic et al does not teach a membrane having up to 3 um pore size and shaped as tubes, fibres, and spiral wounds. The Examiner states that the skilled artisan would have been motivated to use a membrane having up to 3 um pore size and shaped as tubes, fibres, and spiral wounds in such a process because Subramaniam et al teach that those skilled in the art will appreciate that the average pore size can be adjusted to suit the particular application (see Office Action, page 10). Applicant respectfully disagrees for the reasons provided herein below.

Subramaniam et al uses a feed section (12), a precipitation unit (14) which includes a recrystallization chamber (32) and a particle separation section (16). In operation the drug and solvent are introduced by a pump (18) via a nozzle (40) into the precipitation chamber (32) while supercritical carbon dioxide is flowed through an annulus of the nozzle into the precipitation chamber (32) dispersing the drug solution into tiny droplets thereby causing the drug to precipitate (column 6, lines 1-15). Subsequently, the effluent from chamber 32 (the drug, the solvent and the carbon dioxide) is transported to the particle separation section (16) where it enters the separation vessel (42) via an inlet (62) into a filter (56). Pure carbon dioxide is introduced into the chamber (58) of the separation vessel (42) causing a concentration gradient causing the solvent in the feed to pass through the membranes (70 and 72) of the filter (column 6, lines 15-40). The drug particles do not pass through the membrane allowing them to be collected at a later point (column 6, lines 28 and 29). In alternative processes for the particle separation process (column 6, lines 63-67 and column 7, lines 1-67), filter (56) is also used to retain the drug particles while allowing solvent and/or

antisolvent to pass. Thus, the membrane of Subramaniam et al is not used as a precision dosing device but as a means of separating particles from the solvent and antisolvent. Accordingly, Subramaniam et al does not teach or suggest the use of a membrane as a precision dosing device. The use of a membrane as a precision dosing device is taught only in the present invention. Accordingly, Subramaniam et al does not remedy the deficiencies of Jakupovic et al. Withdrawal of this rejection is respectfully requested.

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jakupovic et al in view of Subramaniam et al and further in view of Nocent et al.(*J. Pharm. Sci*, 90, 1620-1627). Applicants traverse this rejection for the reasons provided herein below.

For the reasons stated herein above Jakupovic et al and Subramaniam et al, either alone or in combination, do not render the claimed process obvious. Nocent et al relates to the type of solvent, antisolvent and emulsifier and the concentration of the emulsifier for the production of spherical crystals of salbutamol sulfate (see, abstract). Nocent et al does not does not teach or suggest a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a membrane in a membrane module into one or more antisolvents, or vice versa. Accordingly, Nocent et al does not remedy the deficiencies of either Jakupovic et al and/or Subramaniam et al. Withdrawal of this ground of rejection is respectfully requested.

Claims 1, 8 and 9 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jukapovic et al in view of Sabramaniam et al and in view of Chen et al (US Patent 7,374,779) as evidenced by Nakagawa et al. (*Japan J. Pharmacol.* 29, 509-514, 1979). Specifically the Examiner alleges that Chen et al cures the deficiency of Jakupovic et al and Subramaniam et al by teaching a process for forming progesterone or 3-ketodesogestrel crystal particles. Applicants traverse this rejection for the reasons provided herein below.

Chen et al relates to pharmaceutical formulations and systems for improved absorption and multistage release of active agents. Chen et al generally discusses a variety of techniques for manufacturing the active agent, including crystallization by dissolution in appropriate solvents (see column 54, lines 35-37). The primary focus of Chen et al is formulations and systems for improved absorption of agents. Chen et al does not teach or suggest a continuous antisolvent solidification process which uses a membrane as a precision

dosing device to introduce at least one dissolved organic or inorganic compound in a solvent into one or more antisolvents, or vice versa. Such a teaching is found only in the instant application. Thus, Chen et al fails to cure the deficiencies of either of Jakupovic et al and/or Subramaniam et al. Accordingly, either alone or in combination, Chen et al does not render the claimed invention obvious.

Nakagawa et al relates to anti-inflammatory action of progesterone in a rat model. Nakagawa et al does not teach or suggest a a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a membrane in a membrane module into one or more antisolvents, or vice versa. Accordingly, Nakagawa et al either alone or in combination does not render the claimed invention obvious.

Claims 1, 11 and 12 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jukapovic in view of in view of Sabramaniam et al and Maruyama et al (US Patent 5,512,092,). Specifically, the Examiner alleges that it would have been *prima facie* obvious to modify the teachings of Jakupovic et al and Subramaniam et al. by coating the solid particles, because Maruyama teaches coating pharmaceutical solids utilizing drug coating materials. Applicants traverse this rejection for the reasons provided herein below.

Maruyama et al relates to a method for preparing an aqueous emulsions for coating solid pharmaceutical preparations. In Maruyama an emulsified stock solution is concentrated by removing a part of the liquid components while passing it through a membrane for ultrafiltration (see Maruyama et al abstract). Maruyama et al does not teach or suggest a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a precision dosing membrane into one or more antisolvents, or vice versa. Thus the teachings in Maruyama fail to cure the deficiency in the teachings of Jakupovic and/or Sabramaniam et al as described above.

Claims 1, 18 and 19 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jukapovic in view of in view of Sabramaniam et al and Siam et al (US Patent 6,851,166). Specifically, the Examiner contends that it would have been *prima facie* obvious to modify the teachings of Jakupovic et al and Subramaniam et al. by preparing the dosage in the form of tablets because Saim et al teaches that such particles can be prepared in the form of tablets. Applicants traverse this rejection for the reasons provided herein below.

Saim et al relates to a method of small particle precipitation wherein the solute partyicles are precipitated from a pressurized gaseous fluid or solution or a liquid solution and retained and dispersed in a carrier. Saim et al does not teach or suggest a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a membrane into one or more antisolvents, or vice versa. As Saim et al does not remedy the deficiencies of the cited references, Saim et al does not render the claimed invention obvious. Withdrawal of this rejection is respectfully requested.

CONCLUSION

It is believed that claims are now in condition for allowance, early notice of which would be appreciated. If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. In the event the United States Patent and Trademark Office determines that an additional extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with this filing to Deposit Account No.: 50-4205 ; Reference Number: 2003.817USD1.

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Merck & Co, Inc
2000 Galloping Hill Road
K-6-1-1990
Kenilworth, New Jersey 07033-0530
Tel: (908) 298-7486
Fax: (908) 298-5388

Respectfully submitted,

Carol M. Gruppi

Carol M. Gruppi
Attorney for Applicants
Reg. No. **37,341**